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10/775,964	02/10/2004	Jia-Hwa Fang	PP16502.015	1609

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EXAMINER

FUBARA, BLESSING M

ART UNIT

PAPER NUMBER

1618

DATE MAILED: 11/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/775,964

Applicant(s)

FANG ET AL.

Examiner

Blessing M. Fubara

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 August 2005.
2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 34-44 and 58-61 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5) ☐ Claim(s) _____ is/are allowed.
6) ☒ Claim(s) 34-44 and 58-61 is/are rejected.
7) ☐ Claim(s) _____ is/are objected to.
8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Examiner acknowledges receipt of amendment and remarks filed 08/04/05. Claims 34-44 and new claims 58-61 are pending.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 34-37, 39, 42-44, 58-61 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using cetyl trimethyl ammonium bromide (CTAB) in the preparation of microparticles without washing the prepared microparticles, does not reasonably provide enablement for using all detergents in the preparation of microparticles without washing the prepared microparticles. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following Wands Factors will be considered, namely:

Scope or breadth of the claims;

Nature of the invention;

Relative level of skill possessed by one of ordinary skill in the art;

Level or degree of predictability, or a lack thereof, in the art;

Amount of guidance or direction provided by the inventor; and

Presence or absence of working examples.

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Scope or breadth of the claims: Claims 34, 37, and 39 are directed broadly to producing microparticles by formulating an emulsion in the presence of a detergent and requiring that the formed/prepared microparticles should not be washed and the nature of the invention is microparticles prepared by way of emulsion comprising detergent. However, the scope of enablement provided to one skilled in the art by the disclosure is not commensurate with the scope of protection sought by the claims, because the working examples deal with preparation of microparticles where the microparticles are washed after the microparticles are formed (see Examples 1-5; in those examples, specific detergents (CTAB and PVA) are used and Examples that use detergents other than CTAB and PVA are not taught by the disclosure. Thus, CTAB and PVA are the detergents that are exemplified and not all detergents; furthermore, Examples 1-5 incorporate a washing step. Thus the amount of guidance provided by applicants is preparation of microparticles with a washing step and CTAB and PVA are the detergents. Therefore, the person of ordinary skill in the art would have to perform tremendous amount of experimentation to determine those other detergents that would be suitable in applicants' invention. Also, since Example 6 is the only example, where the microparticles are not specifically disclosed as being washed and where the detergent is again CTAB, one of ordinary skill in the art would have to perform tremendous experimentation with all cationic detergents in order to arrive at the varied cationic detergents that may/would work in addition to the disclosed CTAB. There is thus the absence of working Examples that employ detergents other than CTAB and the guidance provided is therefore limited to CTAB in the amounts taught in the Example 6.

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3. Claims 34-44 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. New claims 58-61 are included in this rejection.

Essential elements are omitted from the claims (See MPEP 2172.01). Paragraph (0025) on page 6 of the disclosure indicates that when the weight of the detergent to the weight of the polymer is from about 0.001:1 to about 0.05:1, filtration or washing step is not necessary in order to remove excess detergent. Further on page 7, and continuation of paragraph (0025), it is stated that when the weight of the cationic detergent, CTAB, to the weight of the polymer, poly (D,L-lactide-co-glycolide), is from about 0.002:1 to 0.04:1, "the microparticles are not subjected to a step to remove excess CTAB from the composition." Thus, the disclosure stipulates that the amount of the detergent to the polymer has to be low (see paragraph 0025 of the disclosure) to avoid a washing step that would remove excess detergent. However, the claim does not indicate the limit of detergent amount at which there would not be a washing step. Furthermore, the cross-flow filtration step where 4 liters of deionized water are used appears to imply a washing step, which may contradict exclusion of a washing step. The scope of the claims is thus not commensurate with what is disclosed to be essential to avoid filtration or washing.

Applicants argue that a conclusion that washing or filtration of the microparticles to remove detergent at higher ratios cannot be compelled by the rules of logic and that the Office is incorrect in stating that the detergent must be low to avoid a washing and that the office lost sight of the fact that claims 34, 37, 39 and 40 do not exclude other methods for removing excess detergent.

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4. Applicants' arguments filed 08/04 have been fully considered but they are not persuasive.

Applicants' statement that "claims 34, 37, 39 and 40 ... do not exclude other method for removing excess detergent, such as filtration step" implies removal of excess solvent by filtration at least. Secondly, it is the disclosure that provided the interpretation that when the amount of the detergent to the polymer has is low the washing step may be avoided. Furthermore, the cross-flow filtration process of claim 36 requires the use of 4 liters of deionized water to remove detergents and this process reads on washing.

Claim Rejections - 35 USC § 102

5. The rejection of claims 34, 35 and 42-44 under 35 U.S.C. 102(e) as being anticipated by Levy et al. (US 6,395,253) is withdrawn because although there is no disclosure as to the exclusion or inclusion of a washing step, the examples disclose a washing step.

6. The rejection of claims 34, 35, 42 and 43 under 35 U.S.C. 102(e) as being anticipated by O'Hagan et al. (US 6,086,901) because the examples disclose a washing step.

However, Levy and O'Hagan render the claims obvious as discussed below.

Claim Rejections - 35 USC § 103

7. Claims 34-44 and 58-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Levy et al. (US 6,395,253) in view of Paliard et al. (US 6,562,346).

LEVY discloses preparation of microspheres that contain DNA or RNA as the bioactive agent (column 4, lines 31, 54 and 55). LEVY prepares a double emulsion of water-in-oil-in-water emulsion by using a condensing agent in one phase and the method comprises the steps of: "(a) dissolving at least one polymer in a water-immiscible organic solvent to yield an organic

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phase; (b) dissolving a polyanionic bioactive agent in aqueous solution to yield a first aqueous phase; (c) emulsifying the organic and first aqueous phases to yield a first milky emulsion; (d) dissolving a condensing agent in aqueous solution to yield a second aqueous phase; (e) emulsifying the first milky emulsion and the second aqueous phase to yield a second milky emulsion; and (f) removing the organic solvent from the second milky emulsion to yield microspheres containing condensed polyanionic bioactive agent. The removal of the organic solvent in the final step is preferably by means of evaporation." DNA and RNA are macromolecules and are polynucleotides. The concept of microspheres meets the microparticle limitation. Regarding the recitation that the microparticles are not subjected to washing step, it is noted that while the examples in Levy disclose a wash step, the basic preparation disclosed by Levy in section 4.2 does not state a wash step but rather that the microspheres are collected by ultracentrifugation and the alternative protocol disclosed in 4.6. Levy uses 0.1% detergent (SDS in this case). There is no demonstration in applicants' specification that not subjecting the microparticles to a washing step provides unusual/unexpected results to the microparticles. The claims do not recite amount of detergent added to make the microparticle in the emulsion.

Regarding claim 36, which is directed to the process of cross-flow filtration, it is noted that in the cross-flow filtration process of the examined application, four liters of deionized water is used to remove the detergents and this appears to be equivalent to washing. There is also no demonstration that the cross-filtration step performed after removing the organic solvent provides unusual results; Levy discloses filtration as one of the steps.

Regarding the ratio of lactide to glycolide, it is noted that there is no demonstration by applicants that the recited ratio provides unusual/expected results. The silence of Levy on the

ratio of lactide to glycolide is an indication that the lactide/glycolide can be used in any desired ratio that would be effective as a condensing agent for the DNA or RNA.

Levy uses SDS detergent. Levy does not disclose the use of cetyl trimethyl ammonium bromide (CTAB) detergent. But Paliard discloses an emulsion that comprises PLG polymer and CTAB (Example 5). Thus Paliard is relied upon for a teaching that the specific CTAB detergent can be used with PLG in an emulsion. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare the double emulsion of Levy where the emulsion comprises a detergent and PLG and a solvent. One having ordinary skill in the art would have been motivated to use the CTAB of Paliard in place of SDS with the expectation that the CTAB will interact with the composition to aid the DNA containing microsphere to disrupt to release the DNA.

8. Claims 34, 35, 36, 42 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Hagan et al. (US 6,086,901).

O'Hagan discloses the process of preparing an emulsion that comprises poly(lactide-glycolide), solvent and detergent (Example 1); O'Hagan discloses that the size of the droplets (particle, microsphere) depends on the ratio of the detergent to oil (column 12, lines 38-47) and also that water-in-oil-water (w/o/w) type emulsion can be formed of the microparticle (column 10, lines 9-20). The process of claim 36 reads on washing because in the cross-flow filtration process, 4 liters of deionized water are used and the removal of the water appears to approximate the process of filtration/washing. While O'Hagan discloses a washing step, there is no demonstration in applicants' specification that not subjecting the microparticles to a washing step provides unusual/unexpected results to the microparticles. Therefore, it would have been

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obvious to one of ordinary skill in the art at the time the invention was made to prepare microparticle according to O'Hagan. One having ordinary skill in the art would have been motivated to do so with the expectation of producing biodegradable microparticles for administration to vertebrates to effect immunization and in the absence of unexpected results, the exclusion of the washing step does not patentably distinguish the invention, which uses 4 liters of water in a cross-flow filtration, over a process that washes the microparticles.

Response to Arguments

Regarding Levy:

The argument as it relates to the 35 USC 103 rejection is addressed. Applicants' argument regarding the washing step has been considered and it is noted that the basic preparation disclosed by Levy in section 4.2 does not state a wash step but rather that the microspheres are collected by ultracentrifugation and the alternative protocol disclosed in 4.6. There is no demonstration in applicants' specification that not subjecting the microparticles to a washing step provides unusual/unexpected results to the microparticles. Secondly, the cross-flow filtration process uses large amounts of water that are removed by filtration and this process reads on washing.

Regarding the argument that 10-90% of the total detergent in the microparticle composition is bound to the microparticle, with the remainder 10-90% unbound, it is respectfully noted that the claims do not recite the starting amount of the detergent to effect the amount bound, and the amount of the bound and the unbound are the same as applicants state. Since there is no specific recitation of the starting amount of the detergent, it would be expected that the same bound/unbound detergent would be expected for the process of Levy. Applicants'

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argument regarding the SDS of Levy has been considered and it is noted that applicants claim detergent in the generic claims and SDS is a detergent. There is no demonstration that the presence of residual detergent on the microparticles, as argued by applicants, provides unusual and unexpected results to the microparticles and have applicants have not demonstrated any unexpected/unusual results. Regarding Paliard, it is noted that Paliard is relied upon for a disclosure that CTAB detergent can be used with PLG in an emulsion. Paliard is not used to provide exclusion of washing.

Regarding O'Hagan as the argument applies to the 35 USC 103 rejection:

In terms of the washing step, it is noted that there is no demonstration that exclusion of a washing step provides unusual/unexpected results and that the presence of residual solvent provides unexpected/unusual results from the microparticles. Regarding the argument that 10-90% of the total detergent in the microparticle composition is bound to the microparticle, with the remainder 10-90% unbound, it is respectfully noted that the claims do not recite the starting amount of the detergent to effect the amount bound, and the amount of the bound and the unbound are the same as applicants state. Since there is no specific recitation of the starting amount of the detergent, it would be expected that the same bound/unbound detergent would be expected for the process of O'Hagan.

9. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Mathiowitz et al. (WO 95,24929) discloses preparation of microparticle in the presence of polyvinyl alcohol by solvent evaporation and the microparticles are not washed (pages 9-12). Biodegradable polymers such as polyanhydride, lactic acid, glycolic acid and poly(lactide-co-caprolactone) are employed.

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10. Suggestion:

The full name cetyl trimethyl ammonium bromide may initially used and the abbreviation CTAB expressed in parenthesis for subsequent use.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Blessing M. Fubara whose telephone number is (571) 272-0594. The examiner can normally be reached on 7 a.m. to 3:30 p.m. (Monday to Friday).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K. Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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